PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ELI LILLY AND COMPANY
P. O. Box 6288
Indianapolis, IN 46206-6288
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.10.2004
Applicant's or agent's file reference X-16014 ✓	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/35969	24.11.2003	27.11.2002

Applicant
ELI LILLY AND COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ullrich, J Tel. +49 89 2399-8048

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-16014	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/35969	International filing date *(day/month/year)* 24.11.2003	Priority date *(day/month/year)* 27.11.2002
International Patent Classification (IPC) or both national classification and IPC C07D487/04		
Applicant ELI LILLY AND COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.11.2003	29.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Steendijk, M Telephone No. +49 89 2399-8460

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/35969

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-120	as originally filed

Claims, Numbers

1-5, 6 (part), 7 (part), 8 (part)	as originally filed
6 (part), 7 (part), 8 (part), 9-13	filed with telefax on 14.10.1994

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 11,13

   because:

   ☒ the said international application, or the said claims Nos. 11,13 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10,12
	No:	Claims	

2. Citations and explanations

   see separate sheet

1) The present application relates to 2-(pyridin-2-yl)-5,6-dihydro-pyrrolo[1,2-b]pyrazole derivatives and ring extended analogues having TGF-beta signal transduction inhibiting activity.

The amendments concern the deletion of the term "prodrug" from claims 9-13 and the reformulation of claim 7 as dependent from claim 1. No amendent to claim 3 has been received; in line with the statement in the response of 14.10.04 this claim is read as relating to "A compound of claim 1 of the formula...".

2) Cited documents:
D1: WO 02/062794 A (GLAXO) 15 August 2002 (2002-08-15)
D2: WO 02/062787 A (GLAXO) 15 August 2002 (2002-08-15)
D3: WO 02/066462 A (GLAXO) 29 August 2002 (2002-08-29)
D4: WO 02/094833 A (ELI LILLY) 28 November 2002 (2002-11-28)

Document D4 was published after the priorities claimed for the present application. On the presumption that the priorities have been validly claimed, this document is herein not considered as prior art.

3) Novelty / Inventive step
Documents D1-D3 relate to pyrazole derivatives having TGF-beta signal transduction inhibiting activity; these compounds lack the characteristic ring-fusion of the presently defined compounds.
It is further noted that document D4 describes related 2-(pyridin-2-yl)-5,6-dihydro-pyrrolo[1,2-b]pyrazole derivatives, which differ however in the definition of the heterocyclic substitution for R2.

The structural difference with the compounds of the closest relevant prior art (D1-D3) may be considered substantial, such that without any further suggestion in the available prior art the person skilled in the art would not consider the presently claimed subject-matter as an obvious solution to the problem of providing further agents that inhibit TGF-beta signal transduction.

Novelty and inventive step may therefore be acknowledged.

4) Further observations
Claims 11 and 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be

formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

11. The method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Claims 1 to 8 or pharmaceutically acceptable salt or ester thereof.

12. Use of a compound according to any one of Claims 1 to 8 or pharmaceutically acceptable salt or ester thereof, in combination with any other anti-cancer agent in the manufacture of a medicament for the treatment of cancer.

13. The method of treating cancer which comprises of administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of Claims 1 to 8 or pharmaceutically acceptable salt or ester thereof in combination with any other anti-cancer agent.

$-(CH_2)_3N(CH_3)_2$;

$-(CH_2)_3N(CH_2CH_3)_2$;

$-(CH_2)X$,

wherein X is either N-morpholino, N-pyrrolidine or N-piperidine;

and the pharmaceutically acceptable salts thereof.

7. A compound according to claim 1 selected from the group consisting of:

a) 2-(Pyridin-2-yl)-3-(thiophen-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole;

b) 5-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-1H-indole;

c) 3-(2-Phenyl-oxazol-5-yl)-2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole;

d) 4-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-benzo[2,1,3]thiadiazole;

e) 5-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]benzo[2,1,3]thiadiazole;

f) 6-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoxaline;

g) 5-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoxaline;

h) 2-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-1H-imidazo[4,5-b]pyridine;

i) 2-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-1H-imidazo[4,5-c]pyridine;

j) 2-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-1H-benzoimidazole;

k) 2-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-oxazolo[4,5-b]pyridine;

l) 2-Dimethylamino-N-[6-[2-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-[1,8]naphthyridin-2-yl]-acetamide;

m) 4-[2-(Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-[1,8]naphthyridine;

k. 3-(4-fluoro-benzofuran-7-yl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole.

l. 7-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-isoquinoline.

m. 1-Methyl-5-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-1H-indole.

n. 1-Methyl-5-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-1H indole.

o. 3-Pyrazin-2-yl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole.

p. 2-(6-Methyl-pyridin-2-yl)-3-pyrazin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole.

q. 3-(2,3-dihydro-benzofuran-5-yl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole.

r. 3-Furan-3-yl-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole.

s. 2-(6-Methyl-pyridin-2-yl)-3-thiophen-3-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole.

t. 3-benzofuran-5-yl-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole.

u. 6-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-pyrazolo[1,5-a]pyrimidine.

v. 3-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole.

9. A pharmaceutical formulation comprising a compound according to any one of Claims 1 to 8 or the pharmaceutically acceptable salt or ester thereof together with a pharmaceutically acceptable diluent or carrier.

10. Use of a compound according to any one of Claims 1 to 8 or pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament for the treatment of cancer, fibrosis, restenosis, wound healing, HIV infection, alzheimer's disease and/or atherosclerosis.